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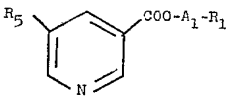
(19)

(54) NEW ESTERS OF SUBSTITUTED NICOTINIC ACIDS

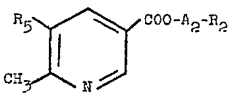
(71) We, THE BOOTS COMPANY LIMITED (formerly known as Boots Pure Drug Company Limited), a British Company, of 1 Thane Road West, Nottingham, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel derivatives of nicotinic acid which have been found to possess biological activity.

According to one aspect of the invention there are provided compounds of general formulae I—IV



I



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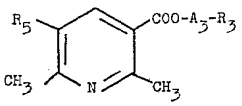

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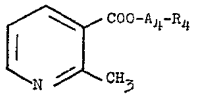


IV

[Price 25p]

and pharmaceutically acceptable acid addition salts thereof in which

R_5 is phenyl;

(a) A_1 is ethylene and R_1 is dimethylamino, 1-pyrrolidinyl, piperidino or 4-methyl-1-piperazinyl, or
(b) A_1 is propylene and R_1 is dimethylamino, diethylamino, 1-pyrrolidinyl, piperidino or morpholino;
(c) A_2 is ethylene and R_2 is diethylamino, 1-pyrrolidinyl, morpholino or 4-methyl-1-piperazinyl, or
(d) A_2 is propylene and R_2 is dimethylamino, morpholino or 4-methyl-1-piperazinyl;
(e) A_3 is ethylene and R_3 is dimethylamino, piperidino or morpholino, or
(f) A_3 is propylene and R_3 is dimethylamino or 4-methyl-1-piperazinyl; and
(g) A_4 is ethylene and R_4 is dimethylamino, or
(h) A_4 is propylene and R_4 is diethylamino, 1-pyrrolidinyl, piperidino or morpholino.

The invention includes pharmaceutically acceptable acid addition salts of the compounds of general formulae I—IV. Typical salts falling within the invention include, for example, hydrochlorides, maleates, succinates and citrates. Details of many specific salts will be found in the examples at the end of this specification, but the acids used therein and which are listed above are only typical acids and are not intended to imply that the invention is limited to salts with these particular acids.

Typical methods for the preparation of the compounds of the invention are as follows:—

[For the sake of brevity, the substituted pyridine nuclei of general formulae I—IV (less the —COO—A—R moeity) will be designated "B" from now on where convenient.]

(1) Trans-esterification of a compound of general formula V

$$B—COOR_6 \quad \ldots V$$

in which R_6 is C_{1-4} alkyl, preferably methyl or ethyl, with the required amino-alcohol of general formula VI

$$R—A—OH \quad \ldots VI$$

in which R represents R_1, R_2, R_3 or R_4 and A represents A_1, A_2, A_3 or A_4. This is carried out by heating such that the alcohol R_6OH which forms is readily eliminated by distillation as it is evolved during the reaction:—

$$B—COOR_6 + R—A—OH \rightleftharpoons B—COO—A—R + R_6OH$$

In this way, and additionally by using an excess of the amino-alcohol as reaction medium, the equilibrium can be displaced towards the required product. Preferably a catalytic amount of sodium should be present.

The temperature required to achieve the desired result and the length of time of heating will naturally vary to some extent with the different values of $B—COOR_6$ and R—A—OH, but, in general, a temperature of at least 70° C. for at least 2 hours is advisable. For preference, to speed up the reaction and to ensure maximum yields, temperatures of the order of 120—180° C. are used for periods of 5—9 hours.

(2) Reaction of an acid chloride of general formula VII

$$B—COCl \quad \ldots VII$$

with the required amino-alcohol of general formula VI hereinbefore described, optionally in an inert organic solvent such as benzene.

(3) Continuous azeotropic distillation with a neutral solvent boiling above 130° C. (preferably 130—160° C.) of a mixture of an acid of general formula VIII

$$B—COOH \quad \ldots VIII$$

and an amino-alcohol of general formula VI hereinbefore described. Examples of suitable solvents are xylene, chlorobenzene, ethylbenzene and cumene.

(4) Pharmaceutically acceptable salts of the bases prepared as described in (1)—(3) above are prepared by conventional methods. Thus, for example, a base may be dissolved in a suitable inert solvent such as a C_{1-4} alkenol (e.g. isopropanol) or tetrahydrofuran and the required acid added. Frequently the desired salt precipitates immediately or upon evaporation of some of the solvent; in other cases the addition of ether is necessary to cause precipitation of the salt.

The starting materials of the aforementioned general formulae V, VII and VIII are prepared by methods known in the art of pyridine chemistry.

It has been found that the compounds of the invention possess vasomotor properties viz. they are peripheral vasodilators, and may be used in the treatment of disorders of circulatory origin.

According to a further feature of the invention there are provided therapeutic compositions which comprise a compound of the invention in association with pharmaceutical excipients for oral, rectal or parenteral administration. The compositions preferably contain 0.1—90% by weight of a compound of the invention.

Compositions for oral administration are the known pharmaceutical forms for such administration, such as for example tablets, capsules, syrups, and aqueous oily suspensions. The excipients used are the excipients known in the pharmacist's art. Thus, for example, tablets comprise a compound of the invention mixed with a conventional diluent such as lactose and a disintegrating agent such as maize starch and a lubricating agent such as magnesium stearate. Such tablets may if desired be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly capsules, for example hard or soft gelatin capsules, containing a compound of the invention, with or without other excipients, may be prepared by conventional means and, if desired, provided with enteric coatings. The tablets and capsules may conveniently contain 10—500 mg. of a compound of the invention.

Compositions for rectal administration are the known pharmaceutical forms for such administration, such as for example suppositories with cocoa butter or polyethylene glycol bases.

Compositions for parenteral administration, e.g. intravenous injection, are the known pharmaceutical forms for such administration, for example sterile solutions in normal saline for injection or sterile solutions in propylene glycol.

It will be appreciated that because of their physical characteristics (crystalline powders), the pharmaceutically acceptable acid addition salts hereinbefore described are to be preferred in most cases to the bases themselves (high boiling liquids).

The compositions hereinbefore described may be provided in dosage unit forms containing 70 mg.-14 g., more usually 140 mg.-1.4 g., optionally in divided dosage unit form.

Disorders of circulatory origin may be treated by a method comprising administering to a subject suffering from such disorders a peripheral vasodilating amount of a compound of the invention. Doses vary according to the activity of the particular compound, but in

general fall within the broad range of 1—200 mg./kg., more usually within the range 2—20 mg./kg.

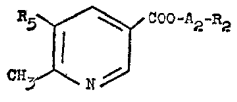
The following non-limitative examples illustrate the invention.

Example 1.

3-*N*,*N*-Dimethylaminoropan-1-ol (13.4 g.) and sodium (0.07 g.) were added to a 100 ml. flask fitted with an inlet for dry nitrogen and provided with distillation means. After heating at about 50° C. until the sodium had dissolved, methyl 5-phenyl-6-methylnicotinate (10 g.) was added and heating continued for 9 hours at about 180° C.; methanol distilled off. After cooling, sodium amino-alcoholate was precipitated by the addition of dry ether (200 ml.) and filtered off. Evaporation of the ether and distillation of the residue *in vacuo* gave 3-*N*,*N*-dimethylaminopropyl 5-phenyl-6-methylnicotinate, b.p. 145—150° C./0.01 mm.

The dihydrochloride was made by conventional means, m.p. 148° C. (isopropanol/ether).

By a similar technique, the compounds listed below were prepared.

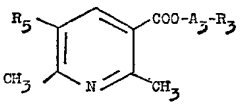


R_2	A_2	b.p. ester (°C./mm.)	Salt	m.p. Salt (°C)
Et_2N—	—$(CH_2)_2$—	165—170/0.01	dihydrochloride	146
	,,	190—195/0.02	,,	180
	,,	200/0.1	,,	178
	,,	210—215/0.1	trihydrochloride	165
	—$(CH_2)_3$—	195/0.02	,,	160
	,,	210—215/0.1	trihydrochloride	204

Example 2.

The apparatus and procedure of Example 1 were used, employing 3-*N*,*N*-dimethylaminopropan-1-ol (15.5 g.), sodium (0.07 g.), ethyl 2,6-dimethyl-5-phenylnicotinate (12.75 g.), and a temperature of 170—180° C. for about 8 hours. There was thus obtained 3-*N*,*N*-dimethylaminopropyl 2,6-dimethyl-5-phenylnicotinate, b.p. 160—170° C./0.15 mm.; citrate, m.p. 70° C. (isopropanol/ether).

The compounds listed below were similarly prepared.

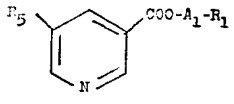


R_3	A_3	b.p. ester (°C./mm.)	Salt	m.p. salt (°C.)
Me_2N—	—$(CH_2)_2$—	160—170/0.1	disuccinate	120
	,,	150—160/0.05	disuccinate	136
	,,	190—195/0.15	dihydrochloride	145
	—$(CH_2)_3$—	210—215/0.1	trisuccinate	110

Example 3.

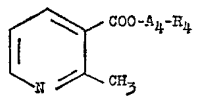
The apparatus and procedure of Example 1 were used, employing 2-*N*,*N*-dimethylaminoethan-1-ol (9 ml.), sodium (0.07 g.), methyl 5-phenylnicotinate (4.1 g.), and a temperature of 120—125° C. for 7.5 hours. The crude 2-*N*,*N*-dimethylaminoethyl 5-phenylnicotinate obtained as an oil was not distilled, but was used directly for the preparation of the maleate, m.p. 126° C. (tetrahydrofuran/ether).

The compounds listed below were similarly prepared.



R_1	A_1	Salt	m.p. salt (°C)
	$-(CH_2)_2-$	maleate	115
	"	"	120
	"	trihydrochloride	200
Me_2N-	$-(CH_2)_3-$	maleate	99
Et_2N-	"	"	144
	"	"	104
	"	"	91
	"	"	69

Example 4.
Using the apparatus and a similar procedure to that of Example 1 the compounds listed below are prepared.



R_4	A_4	b.p. ester (°C./mm.)	Salt	m.p. salt (°C.)
Me_2N—	—$(CH_2)_2$—	65/0.09	maleate	91
Et_2N—	—$(CH_2)_3$—	116—120/0.8	„	99
	„	140—142/0.3	„	96
	„	128/0.05	„	118
	„	130/0.05	„	120

[All the compounds of the invention described in Examples 1—4 gave satisfactory elemantal analyses and their structures have been verified by infra-red spectroscopy.]

Example 5.

In the preparation of tablets, mixtures of the following type may be tableted in conventional manner: —

Pharmaceutically acceptable salt of the invention	10—90%
Lactose	0—80%
Maize starch	5—10%
Magnesium stearate	ca.1%
Microcrystalline cellulose	0—90%
	(by weight)

Example 6.

In the preparation of capsules, a salt of the invention may be mixed with an equal weight of lactose and the mixture encapsulated in hard gelatin capsules.

Example 7.

In the preparation of 1 g. suppositories, bases of the following type may be used, each suppository containing for example 200 mg. of salt of the invention: —

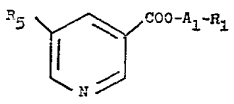
Polyethylene glycol 4000	33%
Polyethylene glycol 6000	47%
Water	20%

Example 8.

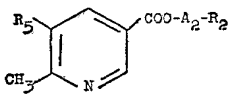
Solutions for parenteral injection may be prepared comprising 4 mg. of a salt of the invention per ml. of normal saline for injection B.P.

WHAT WE CLAIM IS: —

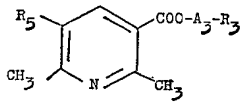
1. Compounds of general formulae I—IV



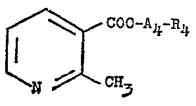
I



II



III



IV

and pharmaceutically acceptable acid addition salts thereof in which

R_5 is phenyl;

(a) A_1 is ethylene and R_1 is dimethylamino, 1-pyrrolidinyl, piperidino or 4-methyl-1-piperazinyl, or

(b) A_1 is propylene and R_1 is dimethylamino, diethylamino, 1-pyrrolidinyl, piperidino or morpholino;

(c) A_2 is ethylene and R_2 is diethylamino, 1-pyrrolidinyl, morpholino or 4-methyl-1-piperazinyl, or

(d) A_2 is propylene and R_2 is dimethylamino, morpholino or 4-methyl-1-piperazinyl;

(e) A_3 is ethylene and R_3 is dimethylamino, piperidino or morpholino, or

(f) A_3 is propylene and R_3 is dimethylamino or 4-methyl-1-piperazinyl; and

(g) A_4 is ethylene and R_4 is dimethylamino, or

(h) A_4 is propylene and R_4 is diethylamino, 1-pyrrolidinyl, piperidino or morpholino.

2. Compounds as claimed in claim 1 and of general formula I in which (a) A_1 is ethylene and R_1 is dimethylamino, 1-pyrrolidinyl or piperidino, or (b) A_1 is propylene and R_1 is dimethylamino, diethylamino, 1-pyrrolidinyl, piperidino or morpholino.

3. 2-(Pyrrolidin-1-yl)ethyl 5-phenylnicotinate and pharmaceutically acceptable acid addition salts thereof.

4. 2-(Pyrrolidin-1-yl)ethyl 5-phenylnicotinate maleate.

5. 3 - Piperidinopropyl 5 - phenylnicotinate and pharmaceutically acceptable acid addition salts thereof.

6. 3-(Pyrrolidin-1-yl)propyl 5-phenylnicotinate and pharmaceutically acceptable acid addition salts thereof.

7. Compounds as claimed in claim 1 and of general formula II in which (a) A_2 is ethylene and R_2 is 1-pyrrolidinyl, morpholino or 4-methyl-1-piperazinyl, or (b) A_2 is propylene and R_2 is dimethylamino, morpholino or 4-methyl-1-piperazinyl.

8. 2 - (4 - Methylpiperazin - 1 - yl)ethyl 6-methyl-5-phenylnicotinate and pharmaceutically acceptable acid addition salts thereof.

9. 2 - (4 - Methylpiperazin - 1 - yl)ethyl 6-methyl-5-phenylnicotinate trihydrochloride.

10. 2 - (Pyrrolidin - 1 - yl)ethyl 6 - methyl-5 - phenylnicotinate and pharmaceutically acceptable acid addition salts thereof.

11. Compounds as claimed in claim 1 and of general formula III in which (a) A_3 is ethylene and R_3 is piperidino or morpholino, or (b) A_3 is propylene and R_3 is dimethylamino or 4-methyl-1-piperazinyl.

12. 2 - Piperadinoethyl 2,6 - dimethyl - 5-phenylnicotinate and pharmaceutically acceptable acid addition salts thereof.

13. 2 - Piperidinoethyl 2,6 - dimethyl - 5-phenylnicotinate disuccinate.

14. 2 - Morpholinoethyl 2,6 - dimethyl - 5-phenylnicotinate and pharmaceutically acceptable acid addition salts thereof.

15. 2 - Morpholinoethyl 2,6 - dimethyl - 5-phenylnicotinate dihydrochloride.

16. Compounds as claimed in claim 1 and of general formula IV in which (a) A_4 is ethylene and R_4 is dimethylamino, or (b) A_4 is propylene and R_4 is diethylamino, 1-pyrrolidinyl or piperidino.

17. 3-Piperidinopropyl 2-methylnicotinate and pharmaceutically acceptable acid addition salts thereof.

18. 3-Piperidinopropyl 2-methylnicotinate maleate.

19. 3-Piperidinopropyl 2-methylnicotinate.

20. 3 - (Pyrrolidin - 1 - yl)propyl 2 - methylnicotinate and pharmaceutically acceptable acid addition salts thereof.

21. 3 - (Pyrrolidin - 1 - yl)propyl 2 - methylnicotinate maleate.

22. A process for preparing the compounds claimed in any one of claims 1—21 substantially as described herein.

23. Therapeutic compositions which comprise as an active ingredient a compound as claimed in any one of claims 1—21 in association with a pharmaceutical excipient for oral, rectal or parenteral administration.

24. Compositions as claimed in claim 23 in the form of tablets or capsules.

25. Compositions as claimed in claim 23 in the form of syrups, aqueous suspensions or oily suspensions.

26. Compositions as claimed in claim 23 in the form of suppositories.

27. Compositions as claimed in claim 23 for parenteral administration.

28 Compositions as claimed in claim 27 in the form of solutions.

29. Compositions as claimed in any one of claims 23—28 in which the active ingredient is in the form of a pharmaceutically acceptable acid addition salt.

30. Compositions as claimed in any one of claims 23—28 in which the active ingredient is 3-piperidinopropyl 2-methylnicotinate or a pharmaceutically acceptable acid addition salt thereof.

31. Compositions as claimed in any one of claims 23—28 in which the active ingredient is 2-(pyrrolidin-1-yl)ethyl 5-phenylnicontinate or a pharmaceutically acceptable acid addition salt thereof.

For the Applicants,
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52 Chancery Lane,
London, WC2A 1HN.

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